

Blinatumomab for the Treatment of Philadelphia Chromosome–Negative, Precursor B-cell Acute Lymphoblastic Leukemia

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Abstract

Blinatumomab is a CD19/CD3 bispecific antibody designed to redirect T cells toward malignant B cells and induce their lysis. It recently gained accelerated approval by the FDA for the treatment of relapsed or refractory Philadelphia chromosome–negative B-cell acute lymphoblastic leukemia (RR-ALL). In the phase II trial that served as the basis for approval, blinatumomab demonstrated significant single-agent activity and induced remission [complete remission (CR) and CR with incomplete recovery of peripheral blood counts (CRh)] in 43% of 189 adult patients with RR-ALL; the majority of responders (82%) also attained negative minimal residual disease (MRD[−]) status that did not generally translate into long-term remissions in most cases. Additional studies show that blinatumomab can induce high response rates associated with lasting remissions in

patients in first remission treated for MRD positivity, suggesting a role for blinatumomab in the upfront, MRD-positive setting. Blinatumomab infusion follows a predictable immunopharmacologic profile, including early cytokine release that can be associated with a clinical syndrome, T-cell expansion, and B-cell depletion. Neurologic toxicities represent a unique toxicity that shares similarities with adverse effects of other T-cell engaging therapies. Further studies are needed to clarify the optimal disease setting and timing for blinatumomab therapy. Additional insights into the pathogenesis, risk factors, and prevention of neurologic toxicities as well as a better understanding of the clinical consequences and biologic pathways that are associated with drug resistance are needed. *Clin Cancer Res*; 21(19); 4262–9. ©2015 AACR.

Introduction

Patients with acute lymphoblastic leukemia (ALL) who experience a relapse after achieving remission or less commonly who are refractory to induction therapy represent a challenging, high-risk population. These patients have poor survival with currently available chemotherapy approaches, and the impact of allogeneic transplant in those selected few that respond to salvage chemotherapy is modest (1–3).

A flurry of targeted therapies have recently been introduced for relapsed or refractory ALL (RR-ALL). Several such approaches are currently under investigation in patients with B-cell precursor ALL (BCP-ALL) and show encouraging results in early-phase clinical trials (Table 1). Most of these therapies target epitopes that are commonly expressed on neoplastic B cells such as CD19, CD20, CD22, and CD52 to induce tumor cell lysis via antibody or complement-dependent cytotoxicity, induce apoptosis, or as a means to effectively deliver cytotoxic compounds to the malignant cell. Another class of drugs, T-cell engaging therapies, are designed to induce neoplastic B-cell destruction by activating specific cytotoxic T-cell responses. This can be achieved by creating autologous T cells with chimeric antigen receptors that have CD19

specificity (CART19) or by the use of blinatumomab, a CD19/CD3 bispecific BiTE antibody. Blinatumomab was the first drug in its class to gain accelerated approval by the FDA for patients with relapsed or refractory Philadelphia-negative ALL (4). We herein review the biologic, pharmacologic, and clinical data that led to the approval of this new drug in ALL and discuss the role of blinatumomab in current clinical practice.

CD19 as a Target

CD19 is a 95-kDa transmembrane protein that appears early during B-cell development and persists throughout B-cell differentiation. CD19 is present on virtually all mature B cells in the blood and in secondary lymphoid tissues; its expression declines only during the late stages of B-cell differentiation toward an antibody-producing plasma cell (5, 6). CD19 acts as a costimulatory molecule of the B-cell receptor (BCR) complex and associates with CD21, CD81, and CD225 to decrease the threshold for BCR-mediated activation of B cells (6, 7). Activation of CD19 results in the phosphorylation of several cytoplasmic tyrosine residues that mediate downstream signaling pathways involved in B-cell function (6, 8). In addition, CD19 was reported to operate in a BCR-independent manner to affect B-cell development, differentiation, and function (5, 6). Uckun and colleagues recently reported on the cloning and characterization of a novel high-mobility group (HMG) box protein as the membrane-associated natural CD19 ligand (CD19-L; ref. 9).

The consequence of CD19 deficiency was previously described in knockout murine models and in humans (10). In one report, a primary immunodeficiency syndrome associated with loss of CD19 expression due to homozygous mutations resulting in

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Table 1. Selected targeted therapies for Ph-negative BCP-ALL

Class	Target	Compound	Stage of clinical development/activity in capsule
Unconjugated antibodies	CD20	Rituximab	FDA approved for various CD20 ⁺ malignancies. Phase II trials in newly diagnosed adult CD20 ⁺ ALL demonstrate survival benefit in younger adults (45, 46). Phase III trial ongoing (GRALL-2005).
	CD20	Ofatumumab	Ongoing phase II trial in newly diagnosed adult CD20 ⁺ ALL (47) ^a .
	CD22	Epratuzumab	Phase II trials demonstrate the benefit of chemotherapy in combination with epratuzumab in pediatric and adult RR-ALL (48-50). Phase III trial ongoing for pediatric patients with relapsed ALL (NCT01802814).
	CD52	Alemtuzumab	Postremission therapy in newly diagnosed adult ALL resulted in deeper MRD response in a phase I trial (51) ^a .
Immunoconjugates	CD22	Inotuzumab ozogamicin	Significant single-agent activity in adults with RR-ALL (52); phase III ongoing and recently reported to have positive results in terms of CR rates (NCT01564784). Ongoing early-phase trials of inotuzumab ozogamicin in combination with chemotherapy in the upfront or RR-ALL setting in adults (53, 54) ^a .
Immunotoxins	CD19	SGN19A	Ongoing phase I study in pediatric and adult patients with RR-ALL/lymphoma (55) ^a .
	CD22	BL22/HA22	Ongoing phase I trial in pediatric RR-ALL (56) ^a .
	CD22, CD19	Combotox	Phase I trials in pediatric and adult RR-ALL completed (57, 58). Combotox in combination with cytarabine currently explored in adults.
T-cell engaging therapies	CD19	Blinatumomab	Accelerated FDA approval for Ph-negative RR-ALL based on phase II trials (31, 32). Effective in eradicating MRD (28-30) ^a . Several phase II and III trials ongoing (e.g., NCT02003222, NCT02143414, NCT02013167, NCT02000427).
Kinase inhibitors	CD19	CART cells	Significant activity in pediatric and adult RR-ALL (40).
	Constitutively activated kinases (Ph-like signature)	Ruxolitinib, dasatinib	Preclinical activity; anecdotal reports from the clinic (59).

^aPresented in abstract form.

deletion of the cytoplasmic domain was described, perhaps pointing to potential toxicities of CD19-targeted therapies. The clinical consequence was of hypogammaglobulinemia and a defective response to antigenic stimuli, albeit with normal composition of the marrow precursor B-cell compartment and peripheral blood B-cell counts (7).

CD19 represents an attractive target in BCP-ALL, as it is present on the vast majority of BCP-ALL cells (11). Furthermore, CD19 is B-cell lineage-specific, and thus targeting this protein does not generally compromise other tissues. There is evidence to suggest a role for CD19 in enhancing malignant pathways (10). For example, high levels of CD19 expression were shown to correlate with Akt activation and overexpression of c-Myc (12, 13). Targeting CD19 *in vitro* seems to confer antitumor activity by induction of cell-cycle arrest (14), apoptosis (9), and sensitization of neoplastic cells to chemotherapy (15, 16).

Blinatumomab: Compound, Pharmacology, and Early Preclinical Observations

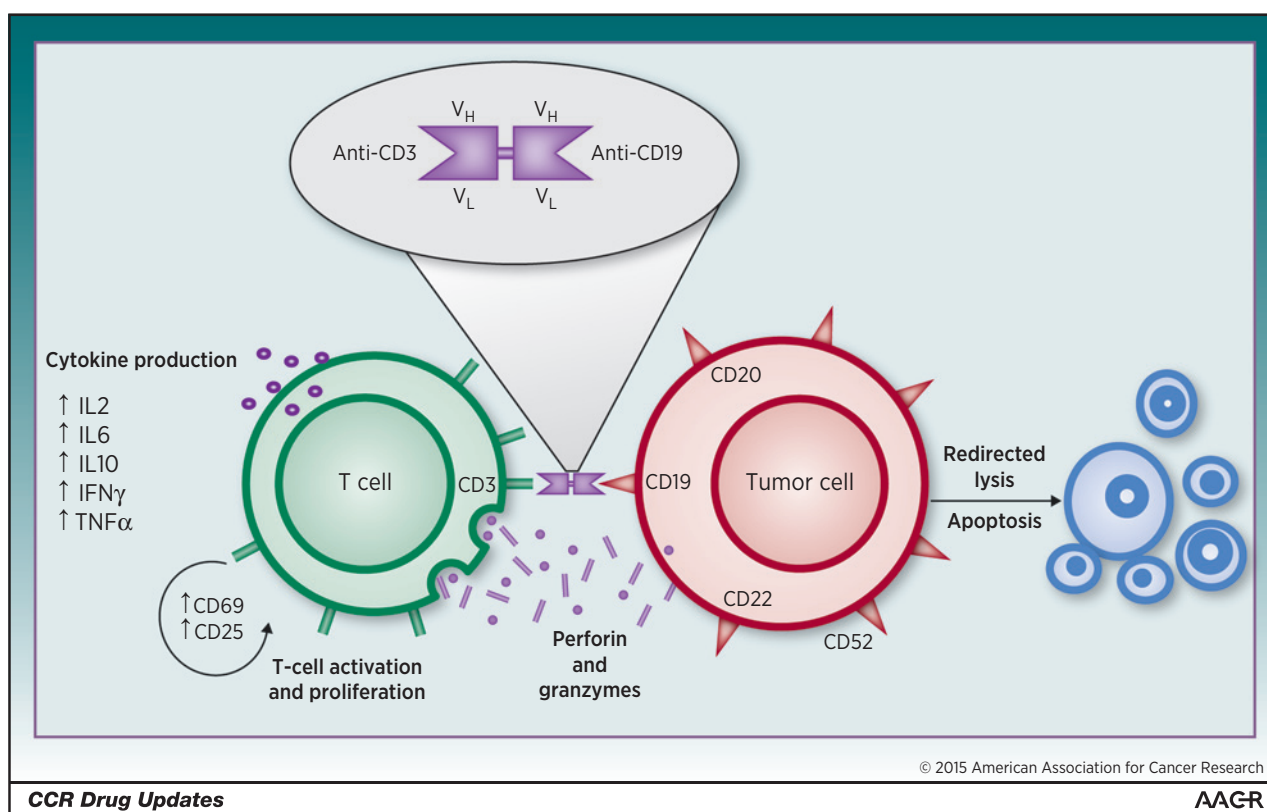
Blinatumomab, a CD19/CD3 bispecific BiTE antibody, is a 55-kDa fusion protein designed to redirect previously unstimulated T cells toward malignant B cells and induces their destruction. The fusion antibody is a construct of two single-chain antibodies that have CD3 and CD19 specificities, respectively, connected by a 5-amino-acid nonimmunogenic linker (ref. 17; Fig. 1).

Initial observations in lymphoma cell lines and later in leukemia and lymphoma murine models demonstrated exceptional efficacy of blinatumomab in eliminating malignant CD19⁺ B cells at very low concentrations (10–100 pg/mL; refs. 18–20). Lysis of the malignant cells is independent of antigen presentation or costimulation and is primarily mediated by the cytotoxic T-cell proteins perforin and granzyme (17). A continuous mode of administration was chosen for human studies based on the drug's

short half-life, mode of action, and disappointing efficacy signals with short-term intravenous infusion schedules in early clinical trials (17).

Blinatumomab is reported to have a predictable, linear pharmacokinetic profile that is independent of the underlying diagnosis (21). In one study, patients with molecularly relapsed or refractory adult BCP-ALL (minimal residual disease positive; MRD⁺) were treated with blinatumomab at a dose of 15 µg/m²/d over a 4-week cycle followed by a 2-week treatment-free interval. The mean steady-state serum concentration with this treatment regimen was 731 pg/mL (range, 492–1,050), the average elimination half-life (*t*_{1/2}) was 1.25 ± 0.63 hours, the average clearance rate was 22.3 ± 5 L/d/m², and the volume of distribution was 1.61 ± 0.74 L/m² (22). Steady-state concentration did not significantly vary between first and subsequent cycles; no human anti-mouse antibodies were detected. In the relapsed refractory ALL (RR-ALL) setting, steady-state concentrations are comparable with those reported above (23); furthermore, similar pharmacokinetic parameters were reported in pediatric patients as compared with adult patients with RR-ALL when body surface area-based dosing was applied (24).

T-cell and B-cell dynamics following administration of blinatumomab are also predictable and well characterized. The initial activation of polyclonal T cells results in a transient release of cytokines such as IL2, IL6, IL10, IFNγ, and TNFα. Cytokine release seems to be confined to the first cycle of therapy, perhaps due to reduction in the number of target cells in subsequent cycles. B-cell counts drop within 2 days of treatment and remain low throughout therapy; T cells decline to nadir within 1 day of treatment but promptly reexpand within a few days to more than double the baseline level after 2 to 3 weeks, mostly attributed to expansion of the effector memory T-cell compartment (CD45RA⁺/CD197⁻). A large proportion of reexpanding T cells also exhibits T-cell activation markers such as CD69 (22, 25).

**Figure 1.**

Blinatumomab structure and mode of action. V_H, heavy chain variable domain; V_L, light chain variable domain.

Blinatumomab for BCP-ALL

To date, treatment with blinatumomab has been reported in RR-ALL or in the setting of MRD positivity. The latter is regarded as a high-risk feature closely associated with disease resistance/relapse (refs. 26, 27; Table 2).

Topp and colleagues (28) initially reported on the outcome of 21 adult patients (median age, 47 years) with MRD-positive disease who were treated with blinatumomab. MRD positivity

was defined as $\geq 1 \times 10^{-4}$ by PCR for immunoglobulin or T-cell receptor genes or specific genetic aberrations (*MLL*, *BCR-ABL*) documented at any time point after consolidation therapy was completed. Fifteen patients had MRD refractory disease and 5 had MRD relapse; 5 patients with Ph⁺ disease were included in this study. Patients on this phase II trial received 15 $\mu\text{g}/\text{m}^2/\text{d}$ continuously during 4 weeks of 6-week cycles; responders were treated with up to 4 cycles. The primary endpoint was defined as the

Table 2. Blinatumomab for ALL

Reference	Context	N	Median age (range), y	Remission rate (CR/CRh)	MRD-negative rate (among responders)	Survival (median follow-up, mo)	Salvaged to transplant
Topp et al. (28, 29)	Phase II: MRD-positive adult ALL	21	47 (20-77)	—	80%	RFS, 65% (33 mo)	50%
Goekbuget et al. (30) ^a	Phase II: MRD-positive adult ALL	116	45 (18-76)	—	80%	NA	NA
Topp et al. (31)	Phase II: Adult RR-ALL	36	32 (18-77)	69%	88%	OS, 9.8 mo (12.1 mo) RFS, 7.6 mo (9.7 mo)	52%
Topp et al. (32)	Phase II: Adult RR-ALL	189	39 (18-79)	43%	82%	OS, 6.1 mo (9.8 mo) RFS, 5.9 mo (8.9 mo)	40%
von Stackelberg et al. (24) ^a	Phase I: Pediatric RR-ALL	41	<18 y	32%	77%	OS, 5.7 mo RFS, 8.3 mo (12.4 mo)	69%
Gore et al. (35) ^a	Phase I-II: Pediatric RR-ALL	39	9 (2-16)	31%	42%	OS, 4.3 mo (6 mo) RFS, 5.6 mo	50%

^aPresented in abstract form.

achievement of PCR-based negative MRD by 4 cycles of therapy. MRD-negative disease was obtained after one cycle in all 16 of the 20 evaluable responding patients (80%), half of whom proceeded to allogeneic transplant. At the time of report, all transplanted patients as well as 4 of 7 who were not transplanted maintained their remission, translating into a relapse-free survival (RFS) rate of 78% at a median follow-up of 13.5 months. Four relapses were documented; 2 were extramedullary relapses and 2 were CD19-negative. The most frequent adverse events were pyrexia, chills, hypogammaglobulinemia, and hypokalemia. Grade III or higher adverse events were documented in 81% of patients, with lymphopenia being the most frequent. No early deaths were observed; 2 patients had neurologic events: seizures in 1 patient and syncope and convulsions in another. An update of this trial reported at 33 months of follow-up demonstrated hematologic RFS of 61% (65% in those transplanted and 60% for those who were not; ref. 29). The preliminary results of a large phase II trial in MRD⁺ ALL patients were recently reported (BLAST trial; ref. 30). Patients ($n = 116$) older than 18 years (median age, 45 years) with ≥ 3 intensive chemotherapy treatments and positive MRD (defined as $\geq 10^{-3}$ by PCR) were treated with the same dose of blinatumomab described above. Seventy-four patients completed planned therapy (4 cycles of blinatumomab or less if the patient went to transplant); 32 patients discontinued therapy due to adverse events, relapse, or investigator decision. The primary endpoint of MRD negativity after 1 treatment cycle was met in 78% of the 113 evaluable patients and further increased to 80% on subsequent treatment cycles. The most frequent adverse events (in $>20\%$ of patients) were pyrexia, headache, tremor, chills, fatigue, nausea, and vomiting. Sixty percent of patients experienced high-grade toxicities, including aphasia and encephalopathy, in 5% each. Two patients died during therapy of subdural hemorrhage and pneumonia.

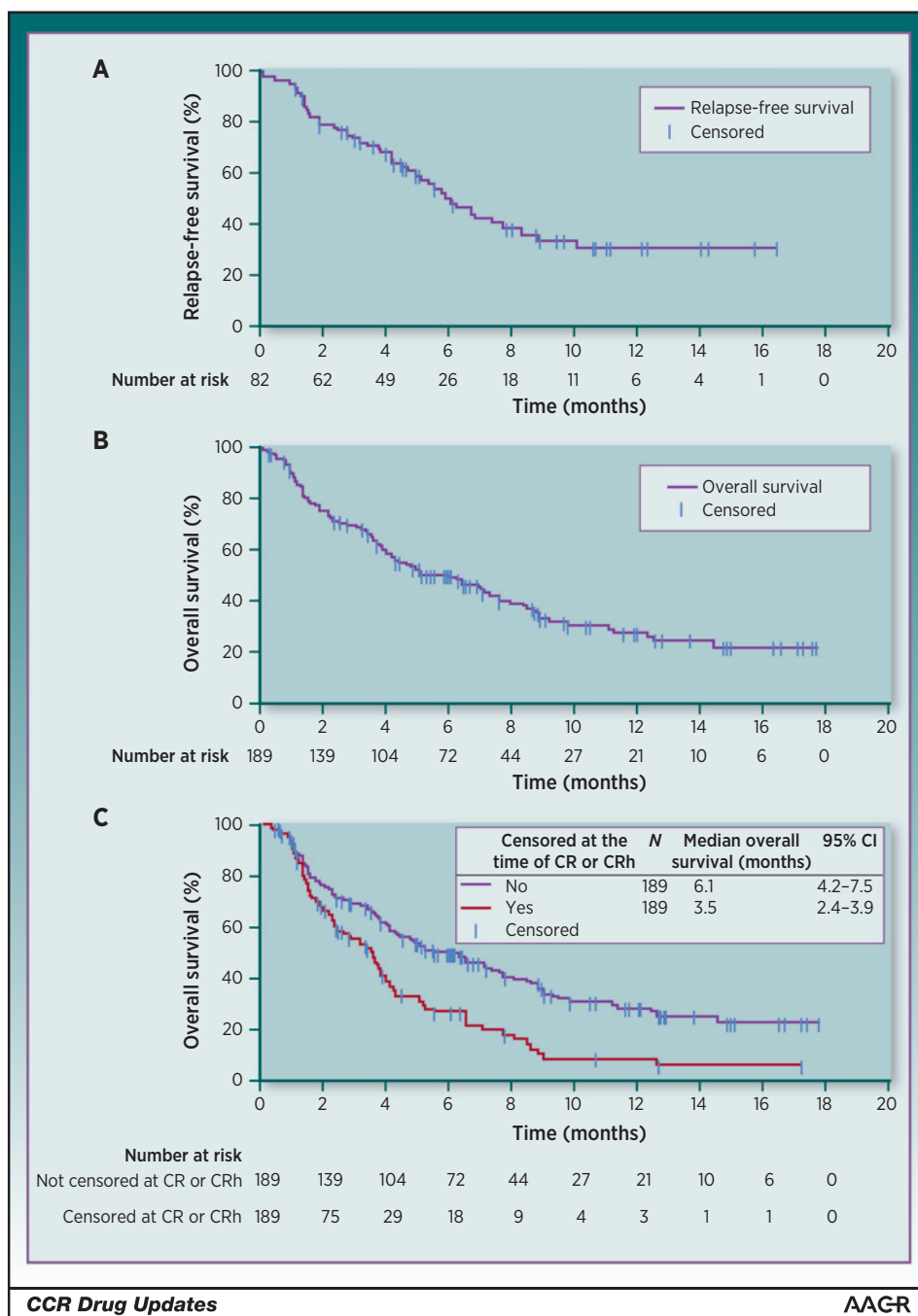
Blinatumomab was also used in the setting of RR-ALL. In an initial publication, Topp and colleagues (31) reported on 36 adult patients (median age, 32 years) treated with blinatumomab for RR-ALL. The study population consisted of high-risk patients and included 15 patients who experienced a relapse after transplant, 8 patients with early relapse or primary refractory disease, 2 patients with Ph⁺ disease, and 4 patients with *MLL* rearranged disease. Patients were initially treated with the "MRD⁺" dose of 15 $\mu\text{g}/\text{m}^2/\text{d}$ for 4 weeks of a 6-week cycle but dosing was later amended because of a grade IV cytokine release syndrome (CRS) in 1 patient to include 1 week of a lower 5 $\mu\text{g}/\text{m}^2/\text{d}$ dose followed by 15 $\mu\text{g}/\text{m}^2/\text{d}$. Dexamethasone or cyclophosphamide pretreatment were also allowed to avoid CRS. The primary end point of this study was defined as the achievement of complete remission [CR; or CR with incomplete count recovery (CRh)] within 2 treatment cycles and was met in 69% of patients; 88% of responders achieved MRD-negative disease. The median overall survival (OS) and RFS were 9.8 and 7.6 months, respectively. Lower CR rates as well as a trend toward lower OS were noted in the posttransplant subgroup. Fifty-two percent of responders went on to receive an allograft with considerable transplant-related mortality (TRM; 6 of 13 patients). Ten patients relapsed, 3 of which had CD19-negative recurrence. Most patients experienced serious adverse events, including 2 cases of grade IV CRS and 6 patients who required treatment interruption due to neurologic toxicities. Six patients died from infection during active treatment. A subsequent phase II study, the largest prospectively reported experience with blinatumomab to date, enrolled 189 adult patients with Ph-negative RR-ALL (median age, 39 years; one third of patients with posttransplant relapse) to receive 28 $\mu\text{g}/\text{d}$ for 4 weeks of a 6-week cycle with a run-in dose of

9 $\mu\text{g}/\text{d}$ on the first week of the first cycle and in up to 5 cycles of therapy. Steroid prophylaxis was given to patients with a high burden of disease [$>50\%$ blasts in marrow, peripheral blasts $>15,000 \times 10^3/\text{L}$ or elevated lactate dehydrogenase (LDH) per investigator discretion]. The primary endpoint of CR/CRh was achieved in 43% of patients; MRD negativity was observed in 82% of responders. Forty percent of responders went on to receive an allograft with a reported TRM of 11% at 100 days, in contrast to the high TRM in the previous trial. OS and RFS were 6.1 and 5.9 months, respectively (Fig. 2); patients who achieved an MRD-negative status tended to have better outcomes (RFS of 6.9 vs. 2.3 months for MRD⁻ and MRD⁺, respectively). Although blinatumomab demonstrated significant single-agent activity in this high-risk disease setting, it should be noted that the OS and RFS were far from satisfactory (with or without transplant). Nonetheless, it is reasonable to perform allogeneic stem cell transplantation (alloSCT) in eligible patients who respond to blinatumomab salvage. Ninety-nine percent of patients had an adverse event of any grade, most frequently (in decreasing order) pyrexia, headache, febrile neutropenia, peripheral edema, nausea, hypokalemia, constipation, and anemia. The majority of patients experienced \geq grade III toxicity (68%), most frequently febrile neutropenia, neutropenia, and anemia; disseminated intravascular coagulation was noted in 2% of patients. Ten percent of patients required dose reductions due to adverse events. Thirty-four patients permanently discontinued therapy due to adverse events, and in 18 patients, dose interruptions were deemed treatment related by the investigator. Twelve percent of patients ($n = 23$) suffered fatal adverse events, mainly infection. Neurologic toxicities were noted in half of the patients and were mostly early in therapy and low grade; 13% of patients had grade III or higher neurologic events that resolved in most cases (32). A phase III trial comparing blinatumomab with investigator's choice of chemotherapy in RR-ALL is ongoing (TOWER study; NCT02013167).

Data on the safety and efficacy of blinatumomab in the pediatric population are still accumulating (33, 34). von Stackelberg and colleagues recently reported on 41 pediatric patients (<18 years of age) treated with blinatumomab at escalating doses for RR-ALL (5–30 $\mu\text{g}/\text{m}^2/\text{d}$). The study population was enriched for patients with high-risk features such as posttransplant relapse (63% of patients) or refractory disease (20%). The recommended dose was established at 5 $\mu\text{g}/\text{m}^2/\text{d}$ for 1 week followed by 15 $\mu\text{g}/\text{m}^2/\text{d}$ for an additional 3 weeks in 6-week treatment cycles. Across all dose levels explored in this study, 32% of patients achieved CR. Seventy-seven percent of responders were rendered MRD-negative and 69% of responders went on to receive a transplant. The median OS (for all patients) and RFS (for responders) were 5.7 and 8.3 months, respectively, with 1 year of follow-up (24). A subsequent report summarized the initial results of a phase II study in pediatric RR-ALL treated with blinatumomab at the above-reported dose (5–15 $\mu\text{g}/\text{m}^2/\text{d}$). CR was achieved in 31% of patients during the first 2 cycles of therapy. Five of the responding 12 patients (42%) were rendered MRD-negative and 6 proceeded to transplant. The median OS (for all patients) and RFS (for responders) were 4.3 and 5.6 months, respectively. CRS was noted in 3 patients (2 of whom had \geq grade III adverse events; ref. 35).

Blinatumomab for Other CD19⁺ B-cell Malignancies

The first pivotal phase I trial to report on the safety and potential efficacy of blinatumomab in blood cancers was published in 2008

**Figure 2.**

RFS (A), OS (B), and OS with censoring at achievement of a CR/CRh (C) in 189 patients with relapsed or refractory BCP-ALL. (Reprinted from ref. 32, *The Lancet Oncology*, Vol. 16, Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al., Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study, 57-66, copyright 2015, with permission from Elsevier.)

and involved 38 adult patients with various refractory CD19-positive lymphomas, mostly mantle cell lymphoma (38.5%) and follicular lymphoma (41%; ref. 25). Blinatumomab was given via continuous intravenous infusion over 4 to 8 weeks at escalating doses from 0.5 up to 60 $\mu\text{g}/\text{m}^2/\text{d}$. Toxicity was generally similar to that described for the ALL cohort above and included manageable adverse events that appeared early in treatment and were largely reversible. Five patients discontinued therapy due to neurologic adverse events. All documented responses occurred at a dose level of $\geq 15 \mu\text{g}/\text{m}^2/\text{d}$, suggesting a dose-response relationship. Eleven of 38 patients (29%) experienced major responses (4 CR and 7

partial remissions). In a follow-up report, additional escalation of the dose to 90 $\mu\text{g}/\text{m}^2/\text{d}$ resulted in 2 documented neurologic dose-limiting toxicities, and the authors recommended a dose of 60 $\mu\text{g}/\text{m}^2/\text{d}$ for treatment of lymphoma (36). Results of a phase II study assessing blinatumomab in heavily pretreated adult patients with relapsed or refractory diffuse large B-cell lymphoma were recently presented. Twenty-five patients were treated, most of whom received treatment with step-wise dosing of 9, 28, and 112 $\mu\text{g}/\text{d}$ for 8 weeks (followed by 4-week consolidation in some). At this higher dose, most patients experienced serious adverse events, most frequently infections; 2 patients died while on study

(progressive disease and pneumonia) and 7 patients suffered grade III neurologic adverse events. The overall response rate was 43% (9 of 21 evaluable patients), and the median duration of response was 11.6 months (37).

Toxicity

Much of the toxicity that is associated with blinatumomab appears early during therapy and stems from its mode of action, that is, polyclonal T-cell activation. Indeed, immunopharmacologic studies demonstrate that blinatumomab is associated with a transient release of inflammatory cytokines and with the proliferation of specific T-cell populations as described above (22). Another anticipated drug effect, B-cell depletion, results in significant hypogammaglobulinemia during and after therapy. All 5 responding patients in one report did not recover to baseline immunoglobulin concentrations based on a median follow-up of over 15 months (38). The clinical consequences of prolonged hypogammaglobulinemia after blinatumomab therapy, as well as the role of replacement therapy in such patients, remain to be established.

CRS and neurologic toxicities deserve special attention, as they seem to be a recurrent theme with T-cell engaging therapies and are frequently reported with blinatumomab as well as with CART19 therapies (39, 40). CRS severity varies among the various reports and can range from mild, low-grade toxicities to life-threatening fatal occurrences. The risk of developing high-grade CRS seems to correlate both with disease burden and initial blinatumomab dosing; the risk of CRS can be significantly reduced with a step-wise dosing approach as well as with a steroid-based pretreatment in patients with high disease burden. In that regard, results from *in vitro* studies suggest that coadministration of dexamethasone with blinatumomab blunts the production of inflammatory cytokines without significantly affecting T-cell activation or neoplastic B-cell killing (41). Furthermore, *ad hoc* analysis from a large phase II trial did not show any appreciable effect of dexamethasone on the achievement of CR/CRh (32). High-grade CRS was not reported in the setting of MRD⁺ ALL (28). In the initial phase II trial in patients with RR-ALL, 2 of 36 patients had grade IV CRS. Both patients had a high burden of disease (~90% blasts in marrow), and one of these patients also had concomitant tumor lysis syndrome. A step-wise dosing approach and pretreatment with steroids and/or cyclophosphamide resulted in no further \geq grade III CRS (31). In the subsequent larger phase II trial, a step-wise dosing approach in the first cycle and steroid pretreatment for patients with $>50\%$ blasts in marrow, peripheral blasts $>15,000 \times 10^9/L$, or elevated LDH per investigator discretion resulted in only 2% of patients ($n = 3$) experiencing grade III CRS (32). In both trials, patients with higher grade CRS seemed to have responded well to therapy (4 of 5 patients achieved CR). Some investigators observed striking clinical and biologic similarities between high-grade CRS after T-cell engaging therapy and hemophagocytic lymphohistiocytosis or macrophage activation syndrome. Furthermore, anecdotal reports describe dramatic responses to IL6 receptor-directed therapy (42), as is the case for CART19 therapies.

In contrast to CRS, neurologic toxicities are reported across diagnoses, disease burden, and dosing levels. These toxicities tend to appear early in therapy (within the first week) and are largely low-grade, reversible, and usually do not necessitate treatment interruption or discontinuation. The clinical presentation can be quite variable and includes tremor, dizziness, confusion, enceph-

alopathy, ataxia, aphasia, and convulsions. The role of dose adjustments or steroids in prevention or management of neurologic toxicities is not clear to date, but nonetheless dose adjustments have been noted in various reports and in the clinic (32, 36). In the largest prospective trial to date, 52% of 189 patients treated for RR-ALL had neurologic adverse events, most of which were low grade (76%). Twenty patients (11%) and 4 patients (2%) had grade III and IV neurologic toxicities, respectively. All of these toxicities resolved, although 3 patients died of apparently unrelated causes after the onset of toxicity. According to dose modification criteria in this study protocol, blinatumomab was discontinued in patients with grade IV neurologic toxicity, those with more than one seizure, and those whose therapy was delayed by more than 2 weeks due to toxicity. All other patients with high-grade neurologic toxicities were eligible for retreatment with blinatumomab at the same or lower dose with steroid premedication once toxicity resolved to grade I or baseline. Applying these criteria resulted in treatment interruption in 29 patients; 10 of these patients already achieved remission before the treatment was interrupted. Forty-two percent of the remaining 19 patients achieved remission after treatment was restarted (32).

Clinical and biologic markers to aid in identifying patients at risk for significant neurologic toxicity are lacking. A low peripheral blood B- to T-cell ratio (e.g., $<1:10$) was suggested in one retrospective analysis to predict neurologic toxicity in lymphoma patients (43). This approach was later applied in patients with non-Hodgkin lymphoma to allocate patients "at risk" for neurologic toxicity to a step-wise dose escalation approach (36).

Conclusions and Future Directions

Blinatumomab represents an important addition to our therapeutic armamentarium for treating RR-ALL and is hopefully the first of many targeted immunotherapies to enter the clinic. Although blinatumomab demonstrated impressive single-agent activity in RR-ALL for which it was approved, current data suggest that responses are generally short-lived and should be followed by allogeneic transplantation if feasible. Unfortunately even those RR-ALL patients in whom MRD negativity was achieved had relatively short RFS (6.9 vs. 2.3 months for MRD⁻ and MRD⁺, respectively; ref. 32), possibly reflecting the inherent resistance due to clonal heterogeneity that characterizes heavily pretreated RR-ALL. In contrast, long-term remissions were reported when blinatumomab was administered for MRD⁺ disease in first remission, suggesting that moving blinatumomab into the upfront setting may be an optimal intervention. Indeed, the phase III E1910 study (NCT02003222) is currently randomizing fit patients to blinatumomab in the postinduction phase. Another ongoing phase II trial is assessing the addition of blinatumomab to low-dose chemotherapy or to steroids and dasatinib in patients older than 65 years with Ph-negative or Ph-positive ALL, respectively (NCT02143414).

Mechanisms of resistance to blinatumomab therapy are poorly described to date. Loss of CD19 expression is a potential pathway for resistance. Indeed, CD19-negative relapses were reported in trials assessing this drug in RR-ALL (31, 32). Furthermore, recent observations suggest that CD19-negative subclones may exist alongside the dominant CD19⁺ clone and thus may be selected for with CD19-targeted therapy (44).

Finally, the unique toxicity profile of T-cell engaging therapies, specifically neurologic toxicity, is poorly understood and studies

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to better describe the "at-risk" population as well as preventive approaches are eagerly anticipated.

Disclosure of Potential Conflicts of Interest

R.M. Stone is a consultant/advisory board member for Amgen and Pfizer. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: O. Wolach, R.M. Stone

Development of methodology: O. Wolach, R.M. Stone

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O. Wolach

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O. Wolach, R.M. Stone

Writing, review, and/or revision of the manuscript: O. Wolach, R.M. Stone

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O. Wolach

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